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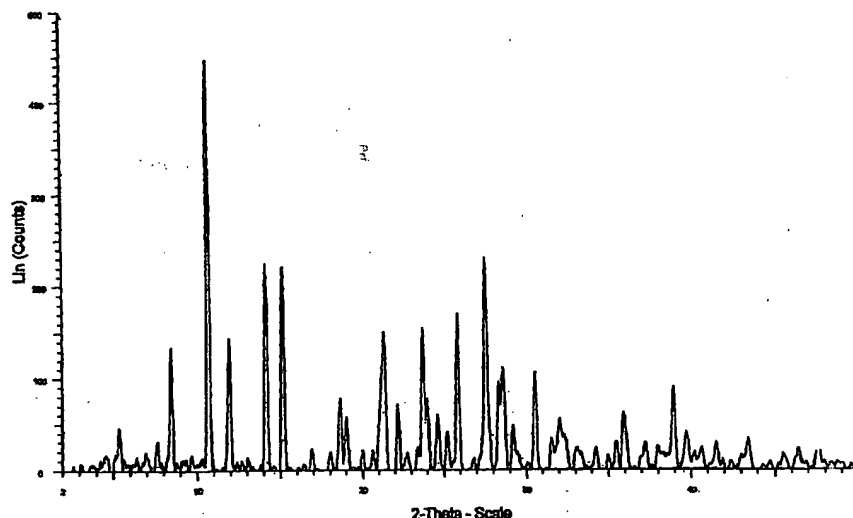
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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

[Continued on next page]

(54) Title: A NOVEL CRYSTALLINE FORM OF CEFDINIR



(57) Abstract: The present invention relates to a novel crystalline form of cefdinir, process for its preparation and to a pharmaceutical composition containing it. Thus, cefdinir is added to water at 20 - 25 °C and then hydrochloric acid (18 %) is added at 20 - 25 °C to get a clear solution. To the solution activated carbon is added at 20 - 25 °C, stirred for 30 minutes, filtered through hyflo bed and washed with water. Then the pH of the filtrate is adjusted to 6.5 with saturated bicarbonate solution at 5 - 8 °C, stirred for clear solution, activated carbon is added and stirred for 30 minutes at 5 - 8°C. The reaction mass is filtered through hyflo bed, washed with water, 1:1 sulfuric acid is dumped to the above solution at 5 - 8 °C (pH: 2.8) and then stirred for 60 minutes at 3 - 5 °C. The resulting solid is filtered, washed with water and dried at 40 °C under vacuum to give cefdinir form H.

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— of inventorship (Rule 4.17(iv))

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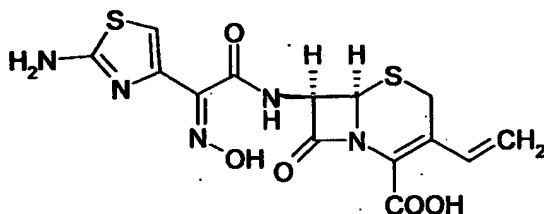
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A NOVEL CRYSTALLINE FORM OF CEFDINIR**FIELD OF THE INVENTION**

5 The present invention relates to a novel crystalline form of cefdinir, to a process for its preparation and to a pharmaceutical composition comprising it.

BACKGROUND OF THE INVENTION

U.S. Patent No. 4,559,334, which is herein incorporated by reference, disclosed
 10 7-substituted-3-vinyl-3-cephem compounds and their pharmaceutically acceptable salts; and their antimicrobial activity. Among them Cefdinir, chemically (6R,7R)-7-[(2Z)-(2-amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid is a third generation cephalosporin antibiotic for oral administration and has a broader antibacterial spectrum than other
 15 orally administrable antibiotics. Cefdinir is particularly effective against staphylococci and streptococci. Cefdinir is represented by the following structure:



As per the process described for preparation of cefdinir in U.S. Patent No.
 20 4,559,334, cefdinir is obtained as amorphous solid.

U.S. Patent No. 4,935,507 described crystalline form of cefdinir and may be designated as form A. The PCT Publication No. WO 98/45299, U.S. Patent Application No. 2004/0242556 A1, PCT Publication No. WO 2004/104010 A1 and U.S. Patent Application No. 2003/0204082 A1 described monohydrate crystalline form of cefdinir and
 25 may be designated as form B. The PCT Publication No. WO 2004/046154 A1 described amorphous cefdinir hydrate. U.S. Patent No. 4,935,507 and U.S. Patent Application No. 2004/0210049 A1 described processes for obtaining some salts of cefdinir such as hydrochloric acid, sulfuric acid, methanesulfonic acid and p-toluenesulfonic acid salts. The PCT Publication No. WO 98/45299 disclosed crystalline solid of cefdinir
 30 dicyclohexylamine salt.

Still there is a need for crystalline form of cefdinir, which can be produced consistently by simple procedures.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of cefdinir, designated as cefdinir form H and typical X-ray powder diffraction spectrum of cefdinir form H is shown in figures 1 and 2.

- 5 Cefdinir form H is characterized by peaks in the powder X-ray diffraction pattern having 2θ angle positions at about 8.4, 10.6, 11.9, 14.1, 15.1, 21.3, 23.7, 25.8 and 27.5 ± 0.2 degrees.

According to one aspect of the present invention, a process is provided for preparation of cefdinir form H, which comprises:

- 10 a) providing an aqueous solution of a cefdinir salt having a pH above 5.0;
 b) adding the above solution to a calculated quantity of an aqueous solution of a mineral acid so as to obtain the reaction mass having the pH of 1.5 - 3.5;
 c) if required adjusting the pH to 2 - 3 with an acid or a base; and
 d) isolating cefdinir form H.

- 15 Preferably the pH of the solution in step(a) is adjusted to 5.0 to 10.0 and more preferably to 6.0 to 10.0.

20 The aqueous solution of a cefdinir salt may be obtained by dissolving cefdinir salt in water and adjusting the pH with an acid or a base if necessary by conventional means. The aqueous solution of a cefdinir salt may be obtained by converting cefdinir in an aqueous medium to the cefdinir salt and adjusting the pH with an acid or a base if necessary by conventional means.

25 The preferable salts used are amine salts such as dicyclohexylamine salts, mineral acid salts such as hydrochloric acid, sulfuric acid, phosphoric acid salts. pH of the aqueous solution may be adjusted to the desired value using an acid or a base as appropriate. An organic or inorganic acid or base may be used. Preferably aqueous sodium carbonate, sodium bicarbonate, hydrochloric acid or sulfuric acid solutions may be used.

30 Preferable mineral acid used in step(b) is sulfuric acid, hydrochloric acid or phosphoric acid. More preferable mineral acid is sulfuric acid or hydrochloric acid.

30 Preferably dilute aqueous acid is used to adjust the pH.

If the pH of the reaction mass obtained above in step (b) is out side the pH range of about 2 - 3, then pH has to be adjusted to 2 - 3 with an acid or a base as appropriate (step c).

The precipitated cefdinir form H is isolated by filtration or centrifugation.

35 According to another aspect of the present invention, a process is provided for preparation of cefdinir form H, which comprises:

- a) providing an aqueous solution of a cefdinir salt having a pH above 5.0;

- b) dumping a calculated quantity of an aqueous solution of a mineral acid to the above solution with stirring at high runs per minutes (RPM) so as to obtain a reaction mass having the pH of 1.5 - 3.5;
- c) if required adjusting the pH to 2 - 3 with an acid or a base; and
- 5 d) isolating cefdinir form H.

Preferably the pH of the solution in step(a) is adjusted to 5.0 to 10.0 and more preferably to 6.0 to 10.0.

The aqueous solution of a cefdinir salt may be obtained by dissolving cefdinir salt in water and adjusting the pH with an acid or a base if necessary by conventional means. The aqueous solution of a cefdinir salt may be obtained by converting cefdinir in an aqueous medium to the cefdinir salt and adjusting the pH with an acid or a base if necessary by conventional means.

The preferable salts used are amine salts such as dicyclohexylamine salts, mineral acid salts such as hydrochloric acid, sulfuric acid, phosphoric acid salts. pH of the aqueous solution may be adjusted to the desired value using an acid or a base as appropriate. An organic or inorganic acid or base may be used. Preferably aqueous sodium carbonate, sodium bicarbonate, hydrochloric acid or sulfuric acid solutions may be used.

Preferable mineral acid used in step(b) is sulfuric acid, hydrochloric acid or phosphoric acid. More preferable mineral acid is sulfuric acid or hydrochloric acid.

The aqueous acid should be dumped at once (step b) and the operation should be carried out at high RPM to ensure thorough mixing of the contents.

If the pH of the reaction mass obtained above in step (b) is out side the pH range of about 2 - 3, then pH has to be adjusted to 2 - 3 with an acid or a base as appropriate (step c).

The precipitated cefdinir form H is isolated by filtration or centrifugation.

Form H obtained as described above processes has water content of 12 - 25% by weight and form H shows the same characteristic powder X-ray diffraction pattern throughout this water content range.

Cefdinir or it's salts used as starting materials may be obtained by processes described in the art, for example by the processes described in U.S. Patent No. 4,559,334, U.S. Patent No. 4,935,507, WO 98/45299, U.S. Patent Application No. 2004/0242556 A1, WO 2004/104010 A1, U.S. Patent Application No. 2003/0204082, WO 2004/046154 A1 and U.S. Patent Application No. 2004/0210049 A1.

The novel crystalline form can be produced consistently reproducibly by simple procedures. The novel crystalline form is obtained polymorphically pure with no or less contamination with other crystalline forms.

The novel crystalline form of cefdinir, form H is useful for preparing pharmaceutical compositions having antibacterial activity. The antibacterial activity of cefdinir is described in U. S. Patent No. 4,559,334 and incorporated herein by reference.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising crystalline cefdinir form H and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is an X-ray powder diffraction pattern of crystalline cefdinir form H of the invention obtained as per the procedure described in example 1.

Figure 2 is an X-ray powder diffraction pattern of crystalline cefdinir form H of the invention obtained as per the procedure described in example 3.

Figure 3 shows the X-ray powder diffraction patterns of the cefdinir form H, form A and form B.

X-Ray powder diffraction spectrum was measured on a Bruker axs D8 advance x-ray powder diffractometer having a Copper-K α radiation. Approximately 1 gm of sample was gently flattened on a sample holder and scanned from 2 to 50 degrees two-theta, at 0.03 degrees two-theta per step and a step time of 0.5 seconds. The sample was simply placed on the sample holder. The sample was rotated at 30 rpm at a voltage 40 KV and current 35 mA.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitations on the scope or spirit of the invention.

Example 1

Step-I:

7-Amino-3-vinyl-3-cephem-4-carboxylic acid (40 gm) and 2-mercapto-1,3-benzothiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-(acetyloxyimino)-acetate (80 gm) are added to tetrahydrofuran (400 ml), stirred for 10 minutes, water (200 ml) is added at 25°C and then the contents are cooled to 15 - 20°C. Triethylamine (20 gm) is added and stirred for 3 - 4 hours at 15 - 20°C. To the reaction mass methylenedichloride (400 ml) is added at 15 - 20°C, stirred for 15 minutes and separated the organic layer. Aqueous layer is treated with activated carbon (4 gm) for 30 minutes while degassing. Filtered over hyflo bed and adjusted the pH of the aqueous layer to 8.1 - 8.5 with K₂CO₃ solution. Ammonium chloride (26.5 gm) is added and stirred at 20 - 25°C for 30 minutes while maintaining the pH at 8.0 - 8.2. The temperature is raised to 35 - 40°C, pH is adjusted to 2.4 - 2.5 with 50% sulfuric acid and stirred for 2 hours at the same temperature. Filtered

the solid, washed with water (400 ml) and dried under vacuum at 40 - 45°C to give 60 gm of crude cefdinir (HPLC purity: 98.1%).

Step-II:

Cefdinir (obtained in step-I) is added to a mixture of water (120 ml) and acetone (600 ml) at 25 - 28°C. Dicyclohexylamine (28 gm) is added to the contents and stirred for 30 minutes at 25 - 28°C (dicyclohexylamine salt of cefdinir precipitates). Then acetone (600 ml) is added to the reaction mass to complete the precipitation and cooled to 0 - 5°C. Filtered the solid, washed with acetone (200 ml) and dried under vacuum at 40 - 45°C to give 90 gm of cefdinir dicyclohexylamine salt. (HPLC purity: 99.2%)

Step-III:

Cefdinir dicyclohexylamine salt (10 gm, obtained in step-II) is added to water (150 ml) at 25 - 30°C, the temperature is raised to 35°C and stirred for 15 minutes at 35 - 40°C. Then activated carbon (1.0 gm) is added to the reaction mass at 35 - 40°C, stirred for 30 minutes at the same temperature, filtered through hyflo bed and washed with water (20 ml). Then the filtrate (pH: 6.8) is added to a solution of aqueous sulfuric acid (50 ml of water + 1 ml of 1:1 H₂SO₄) at 35 - 40°C (pH of the resulting mass: 3.2), the pH is adjusted to 2.5 with sulfuric acid and stirred for 30 minutes. The resulting solid is filtered, washed with 50 ml of water and dried under vacuum at 40°C to give 5.5 gm of cefdinir form H (Moisture Content: 14.5%, HPLC purity: 99.7%). 20 Values and their relative intensities of significant peaks of X-ray diffraction spectrum are listed in table -1.

TABLE - 1

2θ (degree)	Relative Intensity (%)
8.4	30.0
10.6	100
11.9	32.1
14.1	50.2
15.1	49.4
21.3	33.5
23.7	34.4
25.8	37.9
27.5	51.5

Example 2

Cefdinir dicyclohexylamine salt (10 gm) is added to water (175 ml) at 25 - 30°C, the temperature is raised to 35°C and stirred for 15 minutes at 35 - 40°C. Then activated carbon (1.0 gm) is added to the reaction mass at 35 - 40°C, stirred for 30 minutes at the

same temperature, filtered through hyflo bed and washed with water (20 ml). The filtrate (pH: 7.1) is charged into a round bottom flask, the temperature is raised to 35°C and then 3.5 ml of sulfuric acid (1 part conc. H₂SO₄, 4 parts water by weight) is dumped at high RPM (1500 to 2000 RPM) at 35 - 40°C (pH of the resulting mass: 3.0). Then the pH of the reaction mass is adjusted to 2.5 with sulfuric acid (1 part H₂SO₄, 4 parts water by weight) and stirred for 30 minutes at 35 - 40°C. The resulting solid is filtered, washed with 50 ml of water and dried under vacuum at 40°C to give 5.4 gm of cefdinir form H (Moisture content: 16.5%, HPLC purity: 99.8%)

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Example 3

Cefdinir (10 gm) is added to water (150 ml) at 20 - 25°C and then aqueous hydrochloric acid (18%) is added at 20 - 25°C to get a clear solution. To the solution activated carbon (2.0 gm) is added at 20 - 25°C, stirred for 30 minutes, filtered through hyflo bed and washed with water (20 ml). Then the pH of the filtrate is adjusted to 6.5 with saturated bicarbonate solution at 5 - 8°C, stirred for clear solution, activated carbon (1.0 gm) is added and stirred for 30 minutes at 5 - 8°C. The reaction mass is filtered through hyflo bed, washed with water (20 ml), 1 ml of 1:1 sulfuric acid is dumped to the above solution at 5 - 8°C (pH of the resulting mass: 2.8) and then stirred for 60 minutes at 3 - 5°C. The resulting solid is filtered, washed with water (50 ml) and dried at 40°C under vacuum to 6.9 gm of give cefdinir form H (Moisture Content: 18.4%, HPLC Purity: 99.9%)

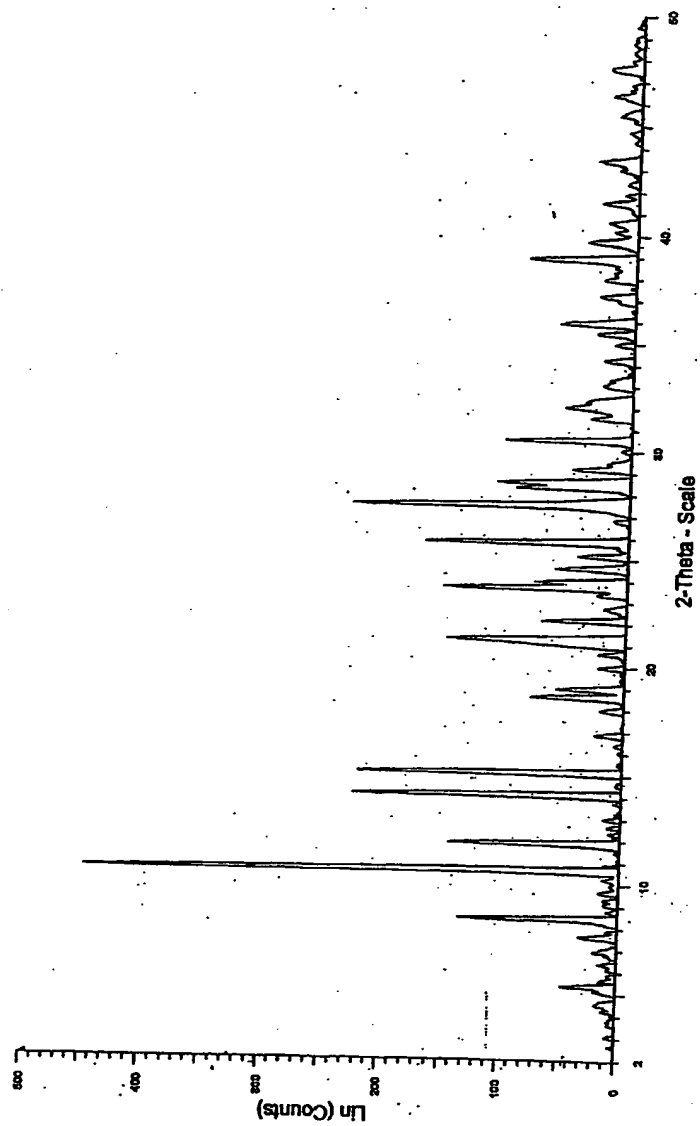
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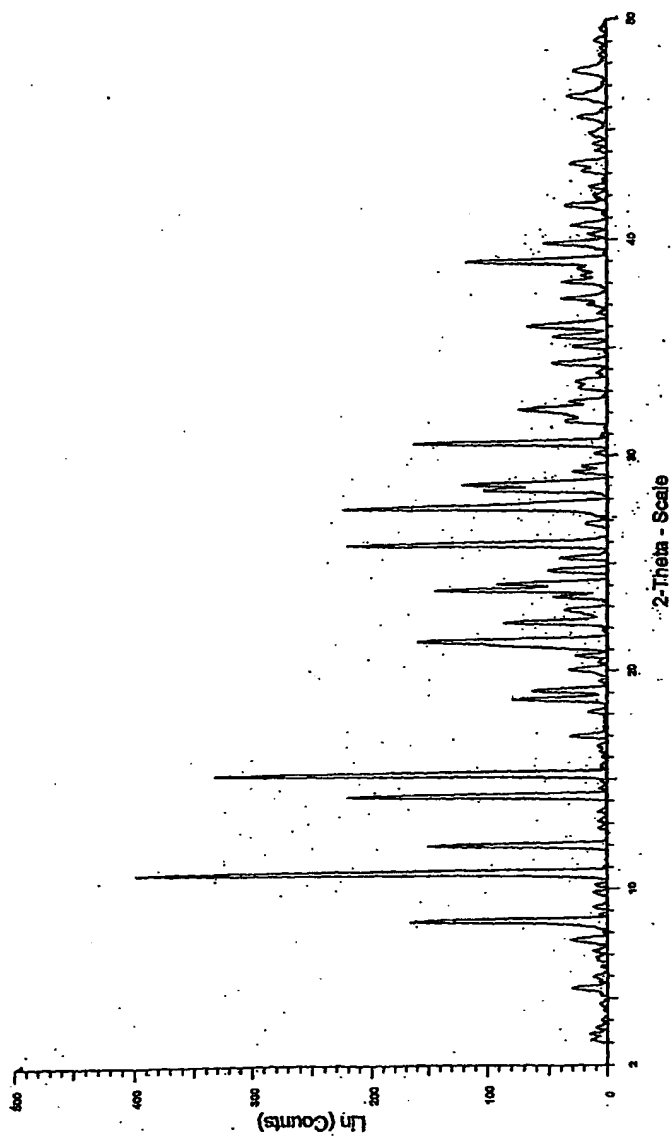
We claim:

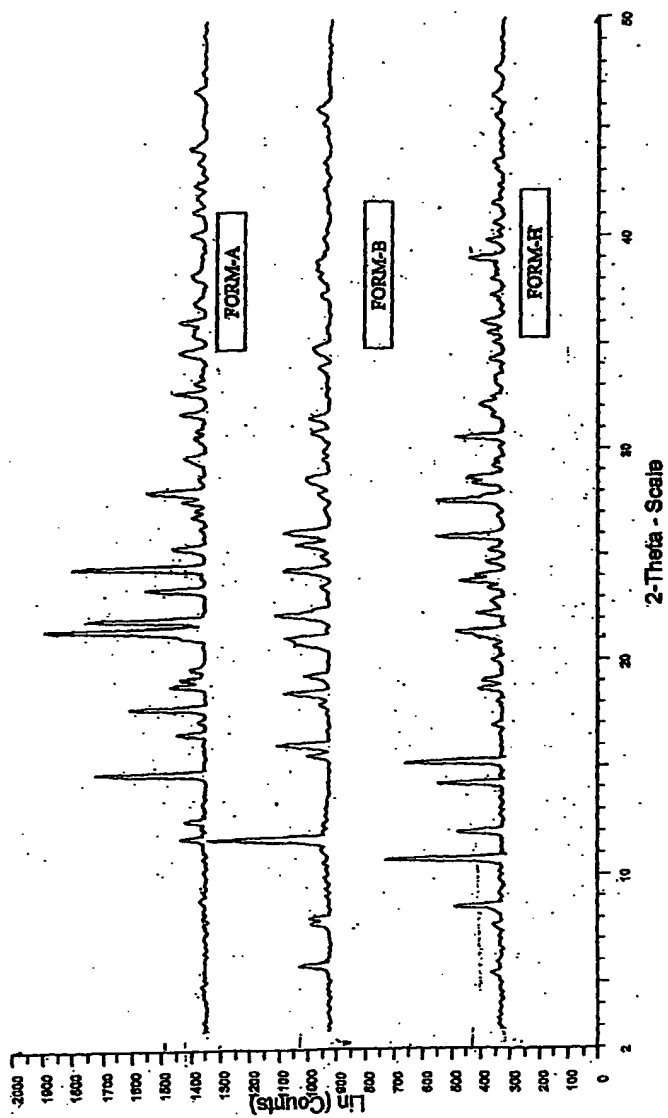
1. A crystalline cefdinir form H, characterized by an X-ray powder diffraction spectrum having peaks expressed as 2θ at about 8.4, 10.6, 11.9, 14.1, 15.1, 21.3, 23.7, 25.8 and 27.5 ± 0.2 degrees.
2. A crystalline cefdinir form H, further characterized by having water content of 12 - 25%.
3. A process for preparation of cefdinir form H as defined in claim 1, which comprises:
 - a) providing an aqueous solution of a cefdinir salt having a pH above 5.0;
 - b) adding the above solution to a calculated quantity of an aqueous solution of a mineral acid so as to obtain the reaction mass having the pH of 1.5 - 3.5;
 - c) if required adjusting the pH to 2 - 3 with an acid or a base; and
 - d) isolating cefdinir form H.
4. The process as claimed in claim 3, wherein the pH of the solution in step(a) is adjusted to 5.0 to 10.0.
5. The process as claimed in claim 4, wherein the pH of the solution is 6.0 to 10.0.
6. The process as claimed in claim 4, wherein the pH of the aqueous solution is adjusted using an acid or a base.
7. The process as claimed in claim 6, wherein the acid is an organic or inorganic acid.
8. The process as claimed in claim 7, wherein the inorganic acid is hydrochloric acid or sulfuric acid.
9. The process as claimed in claim 6, wherein the base is aqueous sodium carbonate or sodium bicarbonate.
10. The process as claimed in claim 3, wherein the aqueous solution of a cefdinir salt is obtained by dissolving cefdinir salt in water and adjusting the pH if necessary.
11. The process as claimed in claim 3, wherein the aqueous solution of a cefdinir salt is obtained by converting cefdinir in an aqueous medium to the cefdinir salt and adjusting the pH if necessary.
12. The process as claimed in claim 3, wherein the salt used in step (a) is an amine salt or a mineral acid salt.
13. The process as claimed in claim 12, wherein the amine salt is dicyclohexylamine salt.
14. The process as claimed in claim 12, wherein the mineral acid salt is selected from hydrochloric acid, sulfuric acid and phosphoric acid.
15. The process as claimed in claim 3, wherein the mineral acid used in step(b) is selected from hydrochloric acid, sulfuric acid and phosphoric acid.

16. The process as claimed in claim 15, wherein the mineral acid used is hydrochloric acid or sulfuric acid.
17. The process as claimed in claim 3, wherein cefdinir form H is isolated by filtration or centrifugation.
- 5 18. A process for preparation of cefdinir form H as defined in claim 1, which comprises:
- a) providing an aqueous solution of a cefdinir salt having a pH above 5.0;
 - b) dumping a calculated quantity of an aqueous solution of a mineral acid to the above solution with stirring at high runs per minutes (RPM) so as to obtain a reaction mass having the pH of 1.5 - 3.5;
 - 10 c) if required adjusting the pH to 2 - 3 with an acid or a base; and
 - d) isolating cefdinir form H.
19. The process as claimed in claim 18, wherein the pH of the solution in step(a) is adjusted to 5.0 to 10.0.
20. The process as claimed in claim 19, wherein the pH of the solution is 6.0 to 10.0.
- 15 21. The process as claimed in claim 19, wherein the pH of the aqueous solution is adjusted using an acid or a base.
22. The process as claimed in claim 21, wherein the acid is an organic or inorganic acid.
23. The process as claimed in claim 22, wherein the inorganic acid is hydrochloric acid or sulfuric acid.
- 20 24. The process as claimed in claim 21, wherein the base is aqueous sodium carbonate or sodium bicarbonate.
25. The process as claimed in claim 18, wherein the aqueous solution of a cefdinir salt is obtained by dissolving cefdinir salt in water and adjusting the pH if necessary.
26. The process as claimed in claim 18, wherein the aqueous solution of a cefdinir salt in step (a) is obtained by converting cefdinir in an aqueous medium to the cefdinir salt and adjusting the pH if necessary.
- 25 27. The process as claimed in claim 18, wherein the salt used in step (a) is an amine salt or a mineral acid salt.
28. The process as claimed in claim 27, wherein the amine salt is dicyclohexylamine salt.
- 30 29. The process as claimed in claim 27, wherein the mineral acid salt is selected from hydrochloric acid, sulfuric acid and phosphoric acid.
30. The process as claimed in claim 18, wherein the mineral acid used in step(b) is selected from hydrochloric acid, sulfuric acid and phosphoric acid.
- 35 31. The process as claimed in claim 30 wherein the mineral acid used is hydrochloric acid or sulfuric acid.

32. The process as claimed in claim 18, wherein precipitated cefdinir form H is isolated by filtration or centrifugation.
33. A pharmaceutical composition comprising crystalline cefdinir form H of claim 1 and a pharmaceutically acceptable excipient.







INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000135

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁷: C07D 501/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁷: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,X	WO 2005/090360 A1 (ORCHID CHEMICALS & PHARMACEUTICALS LIMITED); 29 September 2005 (29.09.2005) <i>examples 5-14, claims 1 and 2, figure 1, page 3 - first paragraph, pages 5, 7 and 8.</i>	1-6, 9-21, 24-33
E,X	US 2005/0215781 A1 (R. CHANDRASEKARAN et al.), 29 September 2005 (29.09.2005) <i>figure 1, page 3 - paragraphs [0028] to [0035], page 2 - paragraphs [0020]-[0023], page 1 - paragraphs [0008]-[0010].</i>	1-6, 9-21, 24-33

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

^a Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search
6 December 2005 (06.12.2005)

Date of mailing of the international search report
19 December 2005 (19.12.2005)

Name and mailing address of the ISA/ AT
Austrian Patent Office
Dresdner Straße 87, A-1200 Vienna
Facsimile No. +43 / 1 / 534 24 / 535

Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000135

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,935,507 A (R. TAKAYA et al.), 19 June 1990 (19.06.1990) <i>examples 1-5, claims.</i>	3-32
A	<i>claims, figure 1.</i>	1, 2, 33
	—	
X	WO 2004/056835 A1 (ANTIBIOTCOS S.P.A.), 8 July 2004 (08.07.2004) <i>example 5.</i>	3-32
A	<i>the whole document.</i>	1, 2, 33
	—	
X	WO 1998/045299 A1 (BIOCHEMIE GESELLSCHAFT MBH), 15 October 1998 (15.10.1998) <i>example 2.</i>	3-32
A	<i>the whole document.</i>	1, 2, 33
	—	
X	WO 2004/104010 A1 (RANBAXY LABORATORIES LIMITED), 2 December 2004 (02.12.2004) <i>examples.</i>	3-32
A	<i>the whole document.</i>	1, 2, 33
	—	
E,X	US 2005/0245738 A1 (G. P. SINGH et al.), 3 November 2005 (03.11.2005) <i>examples - steps "pure cefdinir (I)", page 9 - paragraphs [0125]-[0129].</i>	3-32
	—	
X	WO 2003/050124 A1 (RANBAXY LABORATORIES LIMITED), 19 June 2003 (19.06.2003) <i>example 4.</i>	3-32
	—	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000135

Continuation of first sheet

Continuation No. III:

Observations where unity of invention is lacking

(Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I: claims 1,2 and 33, directed to a particular crystalline cefdinir form (form H) and a pharmaceutical composition comprising this active compound

Group II: claims 3-18, directed to a certain method for the preparation of cefdinir form H.

Group III: claims 19-32, directed to a second method for the preparation of cefdinir form H, differing from that process claimed in claims 3-18.

These three groups of inventions lack - a posteriori (in consideration of the state of the art) unity, since compounds claimed in group I are already known and thus two different preparation methods can no longer be considered to be linked by a single inventive concept.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000135

Patent document cited in search report			Publication date	Patent family member(s)		Publication date	
US	A	20050215781			none		
US	A	20050245738			none		
US	A	4935507		HK	A	18496	1996-02-09
				MX	A1	9203468	1992-09-01
				KR	B1	9708126	1997-05-21
				CA	C	1297096	1992-03-10
				ES	T3	2072856T	1995-08-11
				EP	A2	0304019	1989-02-22
WO	A	1998045299			none		
WO	A	2003050124			none		
WO	A1	2004056835	2004-07-08	EP	A1	1572699	2005-09-14
				AU	A1	2003293746	2004-07-14
WO	A1	2004104010	2004-12-02		none		
WO	A1	2005090360	2005-09-29		none		